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EXAMINER	
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Below is a communication from the EXAMINER in charge of this application

COMMISSIONER OF PATENTS AND TRADEMARKS

ADVISORY ACTION

☒ THE PERIOD FOR RESPONSE:

- a) ☒ is extended to run _____ or continues to run Two months from the date of the final rejection
- b) ☐ expires three months from the date of the final rejection or as of the mailing date of this Advisory Action, whichever is later. In no event however, will the statutory period for the response expire later than six months from the date of the final rejection.

Any extension of time must be obtained by filing a petition under 37 CFR 1.136(a), the proposed response and the appropriate fee. The date on which the response, the petition, and the fee have been filed is the date of the response and also the date for the purposes of determining the period of extension and the corresponding amount of the fee. Any extension fee pursuant to 37 CFR 1.17 will be calculated from the date of the originally set shortened statutory period for response or as set forth in b) above.

☐ Appellant's Brief is due in accordance with 37 CFR 1.192(a).

☒ Applicant's response to the final rejection, filed 8-27-01 has been considered with the following effect, but it is not deemed to place the application in condition for allowance:

1. ☒ The proposed amendments to the claim and/or specification will not be entered and the final rejection stands because:
- a) ☒ There is no convincing showing under 37 CFR 1.116(b) why the proposed amendment is necessary and was not earlier presented.
- b) ☒ They raise new issues that would require further consideration and/or search. (See Note).
- c) ☐ They raise the issue of new matter. (See Note).
- d) ☐ They are not deemed to place the application in better form for appeal by materially reducing or simplifying the issues for appeal.
- e) ☐ They present additional claims without cancelling a corresponding number of finally rejected claims.

NOTE: The amendments to claim 18, 23, 25, 29, 33, 36, 37, 38, 41-43 and the added claim 45-55 require further consideration and possibly additional search

2. ☐ Newly proposed or amended claims _____ would be allowed if submitted in a separately filed amendment cancelling the non-allowable claims.

3. ☒ Upon the filing an appeal, the proposed amendment ☐ will be entered ☒ will not be entered and the status of the claims will be as follows:

Claims allowed: _____
Claims objected to: _____
Claims rejected: 1-53

However;

☐ Applicant's response has overcome the following rejection(s): _____

4. ☐ The affidavit, exhibit or request for reconsideration has been considered but does not overcome the rejection because _____

5. ☐ The affidavit or exhibit will not be considered because applicant has not shown good and sufficient reasons why it was not earlier presented.

☐ The proposed drawing correction ☐ has ☐ has not been approved by the examiner.
☐ Other

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Pending Claims

1. A method of reducing a blood pressure decrease associated with the administration of a liposome to an animal which comprises incorporating a surface agent-modifying lipid comprising a phosphatidylethanolamine conjugated to a dicarboxylic acid into a liposome such that the surface agent-modifying lipid comprises at least about 2 mole percent of the lipid component of the liposome's bilayer and then administering the liposome to the animal wherein an anti-inflammatory agent is administered to the animal prior to administration of the liposome composition and wherein the liposome has an average diameter of from at least about 200 nm to about 5000 nm.
2. The method of claim 1, wherein the anti-inflammatory agent is a steroid.
3. The method of claim 1, wherein the anti-inflammatory agent is a nonsteroidal anti-inflammatory agent.
4. The method of claim 3, wherein the nonsteroidal anti-inflammatory agent is indomethacin.
5. The method of claim 1, wherein the agent is administered to the animal by intravenous or intra-arterial administration.
6. The method of claim 1, wherein the anti-inflammatory agent is administered at most about 30 minutes prior to administration of the liposome composition.

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7. The method of claim 1, wherein the liposome has an average diameter of from about 400 nm to about 1000 nm.
8. The method of claim 1, wherein the liposome is unilamellar.
9. The method of claim 1, wherein the concentration of surface agent modified molecule in the bilayer is at least about 10 mole percent.
10. The method of claim 1, wherein the dicarboxylic acid is succinic acid, glutaric acid, adipic acid, bimelic acid, tartaric acid, mucic acid, tetrafluorosuccinic acid, or hexafluoroglutaric acid.
11. The method of claim 10, wherein the dicarboxylic acid is glutaric acid.
12. The method of claim 1, wherein the phosphatidylethanolamine is dipalmitoyl phosphatidylethanolamine.
13. The method of claim 1, wherein the surface agent-modifying lipid further comprises a functional group capable of attaching to the glycerol backbone of the phosphatidylethanolamine and a functional group capable of attaching to the phosphate group of the phosphatidylethanolamine.
14. The method of claim 12, wherein the functional group is an hydroxyl, thiol epoxide or amine group.

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15. The method of claim 1, wherein the liposome comprises a bioactive agent.
16. The method of claim 15, wherein the bioactive agent is a contrast agent, antibacterial agent, antiviral agent, antifungal agent, anti-parasitic agent, tumoricidal agent, antimetabolite, carbohydrate, polypeptide, peptide, protein, toxin, enzyme, hormone, neurotransmitter, glycoprotein, lipoprotein, immunoglobulin, immunomodulator, vasodilator, dye, radiolabel, radio-opaque compound, fluorescent compound, receptor binding molecule, anti-inflammatory agent, mydriatic compound, local anesthetic, narcotic, vitamin, nucleic acid, polynucleofide, nucleoside, nucleotide, MRI, radio or a water soluble iodinated contrast agent.
17. The method of claim 1, wherein the bioactive agent is a water-soluble iodinated contrast agent selected from the group consisting of iohexol iopamidol, ioxoglate, iotrolan, ioversol, iothalamate, iodimide, iodipamide, iopromide, metrizamide, iopentol, iodixanol, diatrizoate, or iotroxic acid.
18. A method of treating an animal with a bioactive agent comprising administering to said animal an anti-inflammatory agent and a liposome composition wherein said liposome composition induces an adverse physiological reaction in said animal; and reducing said adverse physiological reaction.
19. The method of claim 18, wherein said adverse physiological reaction is a blood pressure drop.
20. The method of claim 19, wherein the anti-inflammatory agent is indomethacin.

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21. The method of claim 18, wherein the anti-inflammatory agent is a steroid.
22. The method of claim 18, wherein the anti-inflammatory agent is non-steroidal.
23. A method of treating an animal with a bioactive agent comprising administering to said animal a composition comprising a liposome and an anti-inflammatory agent, wherein said liposome composition induces an adverse physiological reaction in said animal; and reducing said adverse physiological reaction.
24. A method of treating an animal to reduce adverse physiological reaction in said animal, comprising administering to said animal a composition comprising a liposome and a bioactive agent; wherein said liposome composition induces an adverse physiological reaction in said animal; administering an anti inflammatory agent, to said animal; and reducing said adverse physiological reaction.
25. A liposome composition comprising a liposome and a bioactive agent which is an anti-inflammatory agent.
26. The composition of claim 25, wherein the anti-inflammatory agent is indomethacin.
27. The composition of claim 25, wherein the anti-inflammatory agent is a steroid.
28. The composition of Claim 25, wherein the anti-inflammatory agent is non-steroidal.

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29. A liposome composition comprising a liposome and a bioactive agent which is a contrast agent, in combination with an anti-inflammatory agent.

30. The composition of Claim 29, wherein the anti-inflammatory agent is indomethacin.

31. The composition of Claim 29, wherein the anti-inflammatory agent is a steroid.

32. The composition of Claim 29, wherein the anti-inflammatory agent is non-steroidal.

33. The composition of claim 25, wherein the liposome comprises a lipid bilayer having a lipid and a surface agent modified molecule which comprises an anchor and a surface agent identified molecule, wherein the anti-inflammatory agent is administered to the animal prior to the administration of the liposome composition and wherein the liposome has an average diameter of from at least about 220 nm to about 5000 nm.

34. The composition of claim 25, wherein the liposome has an average diameter of from about 400 nm to about 1000 nm.

35. The composition of claim 25, wherein the liposome is unilamellar.

36. The composition of claim 25, wherein the concentration of surface agent modified molecule in the bilayer is at least about 2 mole percent.

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37. The composition of claim 25, wherein the surface modifying agent is a dicarboxylic acid, a monocarboxylic acid, or a sulfolipid.
38. The composition of claim 25, wherein the surface modifying agent is a dicarboxylic acid.
39. The composition of claim 38, wherein the dicarboxylic acid is a succinic acid, glutaric acid, adipic acid, bimelic acid, tartaric acid, mucic acid, tetrafluorosuccinic acid, or hexafluoroglutaric acid.
40. The composition of claim 39, wherein the dicarboxylic acid is glutaric acid.
41. The composition of claim 25, wherein the anchor is a phosphatidylethanolamine.
42. The composition of claim 41, wherein the phosphatidylethanolamine is dipalmitoyl phosphatidylethanolamine.
43. The composition of claim 25, wherein the surface agent modified molecule comprises a phospholipid anchor having a glycerol anchor and a spacer group and wherein the spacer group comprises a functional group capable of attaching to the glycerol backbone and a functional group capable of attaching to the phosphate group of the phospholipid anchor.
44. The composition of claim 43, wherein the functional group is an hydroxyl, thiol epoxide, or amine group.

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45. A pharmaceutical composition comprising a bioactive agent containing liposome in combination with an anti-inflammatory agent.

46. The pharmaceutical composition of claim 45, wherein the bioactive agent is a contrast agent.

47. The pharmaceutical composition of claim 45, wherein the anti-inflammatory agent is indomethacin.

48. The pharmaceutical composition of claim 45, wherein the liposome comprises a lipid bilayer having a lipid and a surface agent-modified molecule which comprises an anchor and a surface-modifying agent, and wherein the liposome has an average diameter of from at least about 220 nm to about 5000 nm.

49. The pharmaceutical composition of claim 48, wherein the liposome has an average diameter of from about 400 nm to about 1000 nm.

50. The pharmaceutical composition of claim 48, wherein the surface-modifying agent is a dicarboxylic acid, a monocarboxylic acid or a sulfolipid.

51. The pharmaceutical composition of claim 48, wherein the surface-modifying agent is a dicarboxylic acid.

52. The pharmaceutical composition of claim 48, wherein the surface agent modified molecule comprises a phospholipid anchor having a glycerol backbone and a spacer

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group and wherein the spacer group comprises a functional group capable of attaching to the glycerol backbone and a functional group capable of attaching to the phosphate group of the phospholipid anchor.

53. The composition of claim 25, wherein the liposome comprises a bioactive agent.

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